### Venous Thromboembolic Disease Long Term Management



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# DISCLOSURE

Relevant Financial Relationship(s) Speaker Bureau - None Consultant/Research – none

Author – UpToDate (Iron)

Your patients been diagnosis with a thrombosis – now what?



# Post-Thrombotic Syndrome

- Common complication of DVT
- 20-50% of all patients
- 5-10% severe
- Can be disabling





Blood, 19 November 2009, Vol. 114:4624-4631.

# **PTS: Risk Factors**

- Common femoral or iliac vein thrombosis
- Previous DVT
- High BMI
- Older age
- Inadequate initial anticoagulation

# Prevention

- Prevent thrombosis!
- Keep the patient active!
- DOACs
  - 4 studies show less PTS
- Stockings controversial but...

# **Compression Stockings**

- Apply within 24 hours
- 20-30mmHg
- Wear at least 6 months
- Replace every 3 months
- Apply in bed first thing

# **Therapy of PTS**

- Compression stockings
   –Knee high
- Leg elevation
- Horse chestnut seed extract
   BID for a 12 weeks trial
- Treat neuropathic pain
- Leg massage
- Venous stenting (?)

# **Post-PE Syndrome?**

- 50% of patients with PE report dyspnea 6 months later
- 20-70% state health status worse
- Seemingly not related to clot residual or scarring
- Chest pain/discomfort very common
- Warn/reassure patients
- "Cardiac" rehab



**Duration of Therapy** Idiopathic versus provoked thrombosis is the biggest determinant of risk of recurrent thrombosis

# **Duration of Therapy**

- Not all thrombosis are the same
- Can stratify patients by:
  - -Site of thrombosis
  - -Circumstances of thrombosis
    - Most important!
  - Presence of hypercoagulable states

### **Superficial Thrombophlebitis**

- Very common
- Strong inflammatory component
- Wide range of therapeutic options

# STP: LMWH

### STTEPS

- Symptomatic STP
- 8-12 day of therapy
  - Placebo: 30.6% (3.6%)
  - NSAIA: 14.9% (2.1%)
  - 40 mg LMWH: 8.3% (0.9%)
  - 1.5 mg/kg LMWH: 6.9% (1.0%)

#### Vesalio Study Group

- Greater saphenous vein STP
- One month of therapy
  - Prophylactic dose: 7.2%
  - Treatment dose: 7.2%

# **Superficial Thrombophlebitis**

- Fondaparinux 2.5 mg/day x 45 days
  - -Endpoint: F: 0.9% P: 5.9%
  - -DVT/PE F: 0.2% P: 1.5%
  - -No difference in bleeding
  - Need to treat 88 patients to prevent one DVT/PE

-NEJM 363:1222-32, 2010



#### Decousus H et al. N Engl J Med 2010;363:1222-1232

### **Superficial Thrombophlebitis**

- Small and distal: NSAIA and heat
- Painful, large (> 5cm) or greater saphenous vein
  - At least 10 days of prophylactic dose LMWH or fondaparinux
- Role of DOAC uncertain
   –? DVT rate



- Mechanical defects
  - -Catheter
    - PICC 3-5%
  - -Local venous trauma
- Prophylaxis ineffective
- Low risk of serious sequela







- Therapy: PICC Catheter
  - Key is removing catheter
  - No new one for at least 10 days
  - Benefit of anticoagulation uncertain

-25% rate of bleeding

 Remember many are superficial thrombosis



- Therapy: Non-PICC Catheter
  - Line can be removed
    - -Assess need for anticoagulation
  - Line cannot be removed
    - –3 months anticoagulation
      –High rates of serious bleeding

- "Spontaneous"
  - 3 months anticoagulation
  - Look for underlying vascular defects
  - Consider thrombolytic
     therapy

-~75% with underlying lesions



# **Calf Vein Thrombosis**

- High risk of progression
   Up to 10% progression
   PE rate 2-3%
- 12 weeks therapy for most patients

# **Calf Vein Thrombosis Therapy**

Anticoagulation         No anticoagulation         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random,95% CI         M-H, Random,95% CI           Randomized controlled trials         Barrellier, 2010 [44]         3         144         9         141         6.8%         0.31 [0.08, 1.18]           Homer, 2010 [28]         0         35         4         35         2.1%         0.05 [0.00, 0.94]         141           Lagerstedt, 1985 [29]         0         23         8         2.8         2.2%         0.05 [0.00, 0.94]         141           Schwarz, 2010 [8]         2         54         2         53         4.0%         0.98 [0.13, 7.23]           Subtotal (95% CI)         378         387         22.4%         0.37 [0.17, 0.79]         0.45 [0.08, 2.52]           Total events         9         9.99, d.1 = 4 (P = 0.41); l <sup>2</sup> = 0%         550 [1.09, 27.64]         141         24         309         9.6%         0.53 [0.21, 1.32]           Dorr, 2007 [41]         0         20         0         25         Not estimable         142         143         2.0%         0.45 [0.24, 0.70]         144         143         2.0%         0.52 [0.15,		Antiona	gulation			_	Odda Datia	
Randomized controlled trials         Barrellier, 2010 [44]       3       141       6.8%       0.31 [0.08, 1.18]         Barrellier, 2010 [44]       3       141       6.8%       0.31 [0.08, 1.18]         Lagerstedt, 1985 [29]       0       23       8       2.2%       0.010 [0.01, 1.90]         Lagerstedt, 1985 [29]       2       2       53       0.05 [0.00, 0.24]         Sidbtotal (95% CI)       378       387 22.4%       0.37 [0.17, 0.79]         Cohort studies         Brateanu, 2016 [43]       6       141       2.4 (P = 0.01)         Cohort studies         Brateanu, 2016 [43]       6       141       1.30       7.4%       0.55 [0.19, 27.64]         Latropoulos, 2002 [39]       2       19       6       9       0.31       141       2.257 (P = 0.01)         Cohort studies       16.20       16.20	Obudu au Outerran		-					
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Subtotal (95% Cl)       989       1182       77.6%       0.55 [0.31, 0.97]         Total events       80       157         Heterogeneity: $\tau^2 = 0.47$ ; $\chi^2 = 25.70$ , d.f. = 12 (P = 0.01); I^2 = 53%         Total (95% Cl)       1367       1569       100.0%       0.50 [0.31, 0.79]         Total events       89       188         Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); I^2 = 44%       0.01       0.1       1         Test for overall effect: $Z = 2.97$ (P = 0.003)       0.01       0.1       1       10       100								
Total events       80       157         Heterogeneity: $\tau^2 = 0.47$ ; $\chi^2 = 25.70$ , d.f. = 12 (P = 0.01); $l^2 = 53\%$ Test for events       80       157         Heterogeneity: $\tau^2 = 0.47$ ; $\chi^2 = 25.70$ , d.f. = 12 (P = 0.01); $l^2 = 53\%$ Total (95% Cl)       1367       1569       100.0%       0.50 [0.31, 0.79]         Total events       89       188         Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); $l^2 = 44\%$ Heterogeneity:       10         Test for overall effect: $Z = 2.97$ (P = 0.003)       0.01       0.1       1       10		_		-				•
Test for everal offect: Z = 2.07 (P = 0.04)         Total (95% Cl)       1367       1569       100.0%       0.50       [0.31, 0.79]         Total events       89       188         Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); $I^2 = 44\%$ Image: Colored and Colored a	Total events							
Total events         89         188           Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); l <sup>2</sup> = 44%         0.01         0.1         1         10         100	Heterogeneity: $\tau^2 = 0.4$	47; $\chi^2 = 2$	25.70, d.f.	= 12 (P=	0.01); / <sup>2</sup>	? = 53%		
Total events         89         188           Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); l <sup>2</sup> = 44%         0.01         0.1         1         10         100	Test for everall effect:	2 2.07	(P 0.04	)		_		
Total events         89         188           Heterogeneity: $\tau^2 = 0.36$ ; $\chi^2 = 30.26$ , d.f. = 17 (P = 0.02); l <sup>2</sup> = 44%         0.01         0.1         1         10         10	Total (95% CI)		1367		1569	100.0%	0.50 [0.31, 0.79]	•
Test for overall effect: $Z = 2.97 (P = 0.003)$ 0.01 0.1 1 10 100		89		188				
Test for overall effect: $Z = 2.97 (P = 0.003)$ 0.01 0.1 1 10 100		36; χ <sup>2</sup> = 3	30.26, d.f.		0.02); /2	² = 44%	F	
							0.01	0.1 1 10 10
					P = 0.40)	$I^2 = 0\%$	Fav	vors [experimental] Favors [control]

# **Calf Vein Thrombosis Therapy**

	> 6 we	eks	6 wee	eks		Odds Ratio		Odds Ra	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% (	CI M-I	H, Randon	n, 95% Cl	
Ferrara, 2006 [18]	7	96	27	96	35.4%	0.20 [0.08, 0.49]				
Li, 2014 [46]	1	303	2	97	10.2%	0.16 [0.01, 1.75]				
Pinede, 2001 [17]	3	92	2	105	15.9%	1.74 [0.28, 10.62]		-		
Schulman, 1995 [45]	10	171	20	176	38.6%	0.48 [0.22, 1.07]	-	-	•	
Total (95% CI)		662		474	100.0%	0.39 [0.17, 0.90]				
Total events	21		51						J	
Heterogeneity: $\tau^2 = 0$ .				P = 0.1	4); <i>I</i> <sup>2</sup> = 46	<sup>3%</sup> 0	0.01 0.1	1	10	100
Test for overall effect: $Z = 2.20$ ( $P = 0.03$ )							Favors [experim	ental]	Favors [control]	

Fig. 6. Recurrent venous thromboembolism in patients receiving anticoagulant treatment for > 6 weeks versus 6 weeks. CI, confidence interval; d.f, degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]



#### 6 v 12 weeks of rivaroxaban for patients with distal deep vein thrombosis



the**bmj** Visual abstract 🐠

6 additional weeks of rivaroxaban after a 6 week uneventful period of anticoagulation effectively reduces the risk of recurrent thrombosis without increasing the risk of a major bleeding event

Study design	- Randomised contro	lled trial 🛛 🥁 Do	uble blind 🛛 📰 2 year follow-up
iii Population	448 people with symp isolated distal deep ve thrombosis (DVT)	ein Womer	ge 65 years old High risk patients wn cause 42% 94%
Comparison	Randomised		ts received 6 weeks of tandard dose rivaroxaban
	Ri	varoxaban	Control
	20 mg i 200	g once daily for 6 weeks	Placebo for 6 weeks   202
Rivroxaban v placebo		Relative ris	sk 95% Cl
Efficacy (composite)	<b>i</b> 11.5%		<b>i</b> 19.3%
<ul> <li>Isolated distal DV</li> </ul>	/т 🚺 8.0%		<b>i</b> 15.4%
- Proximal DVT	<b>i</b> 1.5%	•	<b>i</b> 3.0%
Pulmonary embo	olism <b>i</b> 2.0%		• 1.0%
Major bleeding	<b>i</b> 0%	•	<b>i</b> 0%
Non-major bleeding	0.5%	•	<b>i</b> 0.5%
EudraCT: 2016-000958-36	K Favours riva	roxaban	Favours placebo >
ClinicalTrials.gov: NCT027		blishing Group Ltd	https://bit.ly/bmj-riv-dvt

Walter Ageno et al. BMJ 2022;379:bmj-2022-072623





# Duration of Therapy: Proximal DVT

- 3 months
  - -Provoked DVT
    - Especially estrogen related
- No benefit with 6 months except more bleeding
- Obtain scan at end of therapy for new baseline

– J Thromb Haemost. 2011 Dec;9(12):2406-10

### **Proximal DVT**



Circulation, May 2001; 103: 2453 - 2460.

# **Residual Thrombosis**

- 3 months 80.5%
- 6 months 61%
- 12 months 42%
- 24 months 31%
- 36 months 27%

#### Prandoni Annals IM 2002

# What is **Provoked**??

- Major
  Limb fracture
  Major trauma
  - -Big surgery
  - -Estrogen
    - Pregnancy
    - Estrogen-containing contraception
    - HRT
  - -Travel


# Idiopathic

- No MAJOR provoking factor
- Minor ones common
  - -Twisted ankle etc..



#### Immobilization

- Classic is bedrest > 72 hrs
- Limb in cast
- Total immobilization > ~ 4 hours
  - –Especially > 10-12 hours

# **Duration of Therapy**

- What is an Idiopathic Thrombosis?
  - No trauma, surgery or hospital stay for 1-3 months
  - No estrogens
  - No long travel (?)
  - No cancer or major risk factors
  - Exact definition controversial

#### 1<sup>st</sup> Idiopathic VTE

- High rates (30-40%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation

 Marked increase in recurrence when stopping anticoagulation

## **BMJ 2019 Meta-analysis**

Year	Risk	Cumulative Incidence
1 Year	10.3%	-
2 year	6.3%	16%
3-5 years	3.8%/year	25% 5 years
6-10 years	3.1/year	36% 10 years

Case fatality rate for recurrence 4% Distal thrombosis 1/10<sup>th</sup> of risk BMJ 2019: 366:4364

### **Extended Therapy**

Treating 1,000 patient-years with extended anticoagulation following acute VTE may result in<sup>a</sup>:



#### Chest 155:1199-1216, 2019

# **Two Phases of VTE Therapy**

Active phase (3 months)

 Prevents reactivation of initial thrombosis

Secondary prevention (> 3 months)

 Prevents new thrombosis
 Need to identify patients who will benefit

• J Thromb Haemo 2012: 10: 507–5

# **D-Dimers**

- D-dimers checked off therapy to predict risk
- Meta-analysis
  - -7 studies
  - Positive D-Dimer: 10%/yr
  - Negative D-Dimer: 2.9 4.0%/yr
- Unclear if repeat testing helps
- Most recent study showed high rates of recurrence with negative D-dimer 5%/yr

# **Idiopathic VTE**

- No good prediction rules
   Negative D-dimer NOT predictive
  - Thrombus resolution NOT predictive
- Still need better prediction rules!
- Safer anticoagulants is shifting balance toward longer treatment

# **Duration of Therapy**

- Indefinite
  - ->1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - -Idiopathic unusual site
  - Idiopathic severe pulmonary embolism
- 3 months

– Provoked pulmonary embolism





### Pregnancy

- Needs weight based LMWH –1 mg/kg BID
- No value in measuring levels
- Hold 24 hours before delivery
- Restart 6-12 after delivery

#### **Breast Feeding**

- Warfarin ok
- LMWH ok
- DOAC NO!





# What about Hypercoagulable States?



#### Hypercoagulable State

- Clear risk factor for 1<sup>st</sup> VTE
- No evidence with classic genetic states predict recurrence
- Multiple guidelines <u>against</u> checking in provoked thrombosis

# **Thrombophilia Work-Ups**

- - -Arterial thrombosis
  - -Upper extremity thrombosis
- **~**\$1200



### Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - -LMWH
  - -Ximelagatran
  - Did not work for warfarin

#### **Apixaban Results**

	Apixaban 2.5mg BID (840)	Apixaban 5mg BID (813)	Placebo (829)
Recurrent VTE	32 (3.8%)	34 (4.2%)	96 (11.6%)
Any Bleeding	27 (3.2%)	35 (4.3%)	19 (2.3%)
Major Bleeding	2 (0.2%)	1 (0.1%)	4 (0.5%)

N = 2482 with VTE (33% PE)

N Engl J Med 2013; 368:699-708

#### **Rivaroxaban Results**

	Rivaroxaban 20mg (1107)	Rivaroxaban 10mg (1127)	Aspirin 100mg (1131)
Recurrent VTE	17 (1.5%)	13 (1.2%)	<b>50 (4.4%)</b>
Any Bleeding	196 (17.8%)	160 (14.2%)	143 (12.8%)
Major Bleeding	6 (0.5%)	5 (0.4%)	3 (0.3%)

N = 3365 50% with PE

N Engl J Med 2017; 376:1211-1222

# **RENOVE Trial**

- RCT of patients with thrombosis
- Randomized 6-24 to standard vs
   low dose anticoagulation
- N = 2768
- Power for bleeding superiority

ASH 2024					
	Full Dose N = 1383	Half Dose N = 1385	HR		
Recurrent VTE	13 (1.9%)	19 (2.2%)	1.32 (NS)		
<b>Clinical Bleeding</b>	154 (15.2%)	96 (9.9%)	0.61 (p <0.5)		
Composite	166 (16.5%)	113 (16.7%)	0.67 (p < 0.5)		

### Lower Dose Therapy

- Only for chronic venous thrombosis!!
- NOT
  - -Atrial fibrillation
  - -Cancer
  - –Bad thrombophilia
  - -Visceral vein thrombosis

# **DOAC VTE Stepped Care**

Acute		
A 10mg BID	6-12 Months	
x 7 Days R 15 mg bid x 21 days	A 5.0 mg BID x 6-12 M R 20 mg qD x 6-12 M	> 6-12 Months A 2.5 mg BID R 10 mg qD

# **Direct Oral Anticoagulants**

- First line therapy for VTE
- Simplified management
- But
  - Patients still need close follow-up
  - -Still need to manage anticoagulants
  - -Expense an issue



#### "Break-Through" Clots

- DOACs are not perfect
- Neither are patients...



#### "Break-Through" Clots

- 1. Is it a breakthrough clot? – New PE in first week ~ 5%
  - -DVT can grow on therapy
  - -New: new vessel or limb involved
  - **–PE after 2 weeks**

-Olson SR, RPTH 2019

"Break-Through" Clots 2. Was patient taking med? -Ideal: levels sent -Ok: INR/PTT check -Check DOAC dose –Ask patient -Check pharmacy

#### "Break-Through" Clots

#### 3. Treatment – LMWH

- If breakthrough LMWH raise dose 25%
- -Warfarin
  - Compliance concerns



# Surgery/Procedures

- Increasing data
- Need to know
  - Drug
  - -Procedure
  - -Renal function



# **DOACs and Surgery**

Drug	Surgery	CrCl	-4	-3	-2	-1	Surgery
Аріх	Major				Hold	Hold	Hold
	Minor					Hold	Hold
Dabig	Major	>50			Hold	Hold	Hold
		<50	Hold	Hold	Hold	Hold	Hold
	Minor	>50				Hold	Hold
		<50		Hold	Hold	Hold	Hold
Rivarox	Major				Hold	Hold	Hold
	Minor					Hold	Hold

# **DOACs:** Post Surgery

- Treat like LMWH
- Simple restart next day
- Complex
  - Prophylactic dose
  - -Full dose 48 hours or more

# Summary

- Keep moving!
- Anticoagulation
  - -3 months or indefinite
- Lower dose DOACs

